In the Claims :

Please add new claims 36 and 37.

36. The molecular circuit of any of claims 1-6, 9-11, and 22-23, wherein the activity of the transcription factor is regulated by a second stimulus other than stress.

37. The molecular circuit of any of claims 15-17, wherein the activity of the first or the second transcription factor is regulated by a second stimulus other than stress.

REMARKS

Claim Amendments

Addition of new claims 36 and 37 is respectfully requested. Support for the new claims is found on p.21, lines 29-30 and on p.22, entire page, and Fig.4.

Rejection of Claims 1-2, 7-26, 28-33 and 35 Under 35 U.S.C. 102(a)

Claims 1-2, 7-26, 28-33 and 35 are rejected under 35 U.S.C. 102(a) as being anticipated by Moonen (WO 9806864). The Examiner cites Moonen for describing « genetically engineered constructs comprising a nucleic acid of interest or a selected gene operably linked to a promoter (constitutive or inducible), preferably [from] a heat shock protein (HSP) [gene], incorporating the construct into an expression vector and introducing the vector into a suitable host cell... » Moonen also teaches that « the specific transcription factor activated during heat shock is often referred to as HSF1 ». Moonen further teaches « that HSF1 trimerizes during stress mediated by HSP70 [The latter concept of mediation by HSP70 is factually incorrect.] and then binds to a consensus nucleotide sequence, the heat shock element (HSE), located within the promoter element of the HSP genes. » Moonen is further credited for teaching « that vectors typically comprise a eukaryotic

transcription unit or an expression cassette that contains all the elements required for the expression of exogenous genes in eukaryotic cells. A typical expression cassette contains a promoter operably linked to the DNA sequence encoding a desired protein and transcription and translation initiation sequences for the regulation of expression of the particular nucleic acid. Moonen teaches the use of cloning vectors such as retroviral vectors, adeno-associated viral.... » [Applicant assumes that the Examiner recognizes that the latter generalized teachings are to be understood in the context of the Moonen invention proper, which concerns the use of HSP gene promoter-driven genes of interest.]

Applicant respectfully but strongly disagrees with the Examiner that Moonen anticipates the present invention. Moonen claims a method of gene therapy using a construct containing a gene of interest that is linked to an Hsp gene promoter. The gene of interest is activated by stressing cells containing the construct, which results in the activation of endogenous HSF1, which factor binds to the HSE sequences contained with the said HSP gene promoter. Thus, Moonen utilizes in his method compositions of matter that are genes of interest linked to and controlled by promoters of HSP genes. Applicant would like to point out that these compositions of matter are not the compositions claimed by the present application. The present application teaches gene switches that are composed of two or three genetic elements that are combined in a novel fashion such that they functionally interact to produce a new regulatory phenotype. This phenotype is the continuous activation of a gene of interest in response to a transient (heat) stress. In some embodiments, the combinations are further modified to allow for the activation of genes of interest in the absence of activation of endogenous HSP genes, or to allow for the disactivation of the genes of interest at an opportune time. In no case, the invention relates to a single element that consists of a gene of interest linked to a promoter of an HSP gene. Except for the type I circuit, no composition even includes an element consisting of a gene of interest linked to a promoter of an HSP gene. It is noted that the term « gene of interest » is not defined in the Moonen application. It is assumed for the

purpose of this discussion that the term is synonymous with « therapeutic genes » and « selected structural genes ». This is supported by the description of genes that can be used with the invention, which genes are without exception structural genes, i.e., genes encoding enzymes and other structural proteins (p.5, line 18 ; p.15, line 5, p.25, line 35 ; p,26, line 1 ; p.27, line 26, p.28, line 33 ; p.29, line 16 ; p.30, line 23 ; claim 6).

To elaborate on the above remarks, in a representative embodiment the present invention relates to a molecular circuit or gene switch (and a gene of interest) that comprises a gene for a transcription factor that is functionally linked to a promoter that is activated by stress and by the transcription factor, and a gene of interest that is functionally linked to a promoter that is activated by the transcription factor (see claim 1). Clearly, this combination of genetic elements does not correspond to the single element described by Moonen. The gene switches of the present invention all produce a novel regulatory phenotype (and variations thereof) that cannot be achieved with the HSP promoter-driven genes of interest of Moonen, namely the sustained activation of a gene of interest subsequent to a transient activating stress. Because of the well-known feedback regulation of HSP genes, HSP gene promoters lose activity shortly after termination of the activating stress treatment. The switches of the present invention avoid this feedback regulation, which is severely hampering the utility of HSP promoters as gene switches, by the introduction of a counterbalanced positive feedback loop : a transient stress is used to activate a transcription factor gene. The transcription factor made during this activation phase not only transactivates the gene of interest but also transactivates its own gene. As a consequence, transactivator continues to be synthesized even after recovery of the cells from the activating stress, and the gene of interest remains active for an extended period, potentially indefinitely. The positive feedback loop that maintains transactivator expression is counterbalanced by degradation of the transactivator, ensuring that the activity of the circuit is proportional to the intensity of the initial stress. These properties of the gene switches of the present invention are novel

and are not present in the single-component switches of Moonen. Indeed, the switches of the present invention were intended to overcome the severe shortcomings of the type of switches described by Moonen. In light of this discussion, withdrawal and reconsideration of the rejection is respectfully requested.

Rejection of Claims 3-6 Under 35 U.S.C. 103(a)

Claims 3-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moonen in further view of Zuo et al. Applicant fails to understand the Examiner's argument but wishes to make the following observations relating to the appropriateness of a 103-type rejection. Moonen describes genes of interest that are functionally linked to HSP gene promoters. Zuo et al, describe mutant HSF1 that are constitutively active transcription factors as well as a chimeric HSF, LexA(87)-hHSF1(79). It is applicant's position that a 103(a) rejection of claims 3-6 is not legally proper. First, if a conclusion of obviousness were based on the Moonen reference alone, a showing would need to be made of a suggestion or motivation to modify the teachings of that reference to the claimed invention. B.F. Goodrich, 72 F.3d at 1582, 37 USPQ2d 1673, 1680 (Fed.Cir. 1988). Similarly, if a conclusion of obviousness were to be based on Moonen in view of Zuo, one of the references would need to provide motivation to combine its techings with the other. See Tec-Air, Inc., 192 F.3d at 1359, 52 USPQ2d at 1298. Neither of the references contain anything to would motivate its combination with the other. Such combination could only be made in hindsight. See In re Fine, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988). Second, even if a combination of the teachings of the two references could properly be made, such combination would not result in Applicant's invention. No plausible argument could be made that combination of Moonen's HSP promoter-driven genes and Zuo's mutant HSF1 will lead the skilled person to imagine circuits comprising a combination of genetic elements that are assembled in such a way that the novel regulatory phenotype of the invention results. As also discussed before, the

essence of the invention of the circuits are the novel ways in which different genetic elements are combined to produce new regulatory properties. In light of this discussion, withdrawal and reconsideration of the rejection is respectfully requested.

Rejection of Claim 27 Under 35 U.S.C. 103(a)

The Examiner states that the method of claim 27 of producing a protein of interest using cells containing the regulatory circuits of the invention is obvious based on Moonen and in further view of Bailey et al. The Applicant respectfully disagrees. As discussed above, Moonen stands for the use of constructs containing a gene of interest controlled by an HSP gene promoter. Moonen does not describe the regulatory circuits or gene switches of the present invention. Bailey et al. describes the use of baculovirus vectors as vehicles for gene transfer. The combination of the two references cannot obviate claim 27. At most it could render obvious a claim to delivery of genes of interest controlled by an HSP gene promoter. This is not the subject matter of claim 27. Withdrawal and reconsideration of the rejection os respectfully requested.

CONCLUSION

It is respectfully submitted that the rejections made by the Examiner are legally improper. Thus, the Examiner is respectfully requested to reconsider the rejections and to withdraw them. Applicant believes that the claims presently are in condition for allowance.

If the Examiner feels that a telephone conversation with Applicant who acts as its own Attorney (Reg.No. 40,859) would be helpful in expediting the prosecution of this case, the Examiner is encouraged to call Applicant at (305) 243-5815/6.

Respectfully submitted,

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